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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/067,996	02/08/2002	Ruiping Liu	MEMORY-2	9946

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EXAMINER	
HABTE, KAHSAY	

ART UNIT	PAPER NUMBER
1624	8

DATE MAILED: 06/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/067,996	LIU ET AL.	
	Examiner	Art Unit	
	Kahsay Habte, Ph. D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *5/23/03* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33,36-73 and 75* is/are rejected.

7)☒ Claim(s) *34,35 and 74* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4&5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 1-75 are pending.

Election/Restriction

2. Applicant's election of single disclosed species (page 60, line 24) in Paper No.7 is acknowledged. Since the examiner did not find any prior art on the single disclosed species, the search has been extended to cover the entire genius.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-49 and 75 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 45, it has been recited a method of treating cognition impairment or decline, but the specification is not enabled for such a scope.

Cognitive impairment - are disorders in a brain that prevents someone from thinking well, from solving problems, or from storing information. Three main types of cognitive impairments are: Delirium, Dementia, and Amnesia.

Dementia is a label for a cluster of symptoms involving deterioration in behaviors such as memory, language, and reasoning. The deterioration results from a disease process in the brain. The disease progresses from mild through severe stages and interferes with the ability to function independently in everyday life. Dementias are fatal medical diseases that have major psychosocial consequences.

Dementia is classified as cortical or subcortical depending on the area of brain affected.

Cortical dementia causes problems in memory, thinking, and language. Alzheimer's Disease is a disorder that causes cortical dementia. The cognitive problems, depending on their nature, are called aphasia, apraxia, amnesia, and agnosia. These problems may include difficulty finding words, difficulty comprehending written or spoken material, and even mutism. Speech, which is the machinery for sound, is usually normal; however, it is the language component that breaks down. The memory problem is often an inability to learn new information.

Insight into the condition is usually absent and a person's mood is unconcerned or uninhibited. The motor system is normal, at least in the early stages.

Subcortical dementia affects parts of the brain below the cortex and is characterized by slowing, difficulty in retrieving information from memory, and altered mood. Parkinson's disease and multiple sclerosis are examples of a condition that can result in a subcortical dementia. Language ability is usually normal, although speech is dysfunctional and the motor system may result in stooped or extended posture, increased muscle tone, and tremors. Memory problems are due to a difficulty in

retrieving information that is in fact learned. The person's mood may be either apathetic or depressed, and insight into the condition is usually present.

Delirium is a condition of severe confusion and rapid changes in brain function, usually the result of treatable physical or mental illness.

Acute confusional states are usually the result of a physical or mental illness and are usually temporary and reversible.

Delirium involves a rapid alternation between mental states (for example, from lethargy to agitation and back to lethargy), with attention disruption, disorganized thinking, disorientation, changes in sensation and perception, and other symptoms.

Disorders that cause delirium are numerous and varied. They may include conditions that deprive the brain of oxygen or other substances. Delirium may be caused by diseases of body systems other than the brain, by poisons, by fluid/electrolyte or acid/base disturbances, and by other serious, acute conditions.

Mental retardation - is described as below-average general intellectual function with associated deficits in adaptive behavior that occurs before age 18. Causes of mental retardation are numerous, but a specific reason for mental retardation is determined in only 25% of the cases. Failure to adapt normally and grow intellectually may become apparent early in life or, in the case of mild retardation, not become recognizable until school age or later. An assessment of age-appropriate adaptive behaviors can be made by the use of developmental screening tests. The failure to achieve developmental

milestones is suggestive of mental retardation. A family may suspect mental retardation if motor skills, language skills, and self-help skills do not seem to be developing in a child or are developing at a far slower rate than the child's peers. The degree of impairment from mental retardation has a wide range from profoundly impaired to mild or borderline retardation. Less emphasis is now placed on degree of retardation and more on the amount of intervention and care required for daily life.

Causes of mental retardation can be roughly broken down into several categories:

- unexplained (This category is the largest and a catchall for undiagnosed incidences of mental retardation.)
- trauma (prenatal and postnatal)
- infectious (congenital and postnatal)
- chromosomal abnormalities
- genetic abnormalities and inherited metabolic disorders
- metabolic
- nutritional
- environmental

As shown above, since the origin and nature of mental retardation is different one from the other, it is impossible to treat mental retardation in general.

Major depression – is an important type of cognitive disorder.

Autism - is a cognitive disorder as discussed above that has no effective pharmacological treatment to this day.

4. Claims 37-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claim 37, it has been recited a method of enhancing cognition, but the specification is not enabled for such a scope.

Note that the method of enhancing cognition is the same as treating cognitive disorders. Please see enablement rejection in paragraph 4.

5. Claims 45 and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating most of the diseases recited in claim 49, does not reasonably provide enablement for the treatment of memory impairment due to Alzheimer's disease, Parkinson's disease, stroke or cardiovascular disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. It has been recited the treatment of memory impairment due to Alzheimer's disease, Parkinson's disease, stroke or cardiovascular disease, but the specification is not enabled for such a scope.

The central characteristic of Alzheimer's disease is the deficiency in the level of the neurotransmitter Acetylcholine that plays an important role in memory. Alzheimer's disease can be treated only by Acetylcholinesterase inhibitors that reduce the depletion of acetylcholine. The skill level in the art is so low that the only treatments available to this day are drugs that inhibit Acetylcholinesterase.

Parkinson's disease is a neurological disorder that is also characterized by rhythmic muscle tremors, hypokinesia, and muscular rigidity. Dopamine, a hormonelike substance is an important neurotransmitter in both the central and peripheral nervous systems that is currently used as treatment for Parkinsonism. Dopamine is a neurotransmitter involved in the regulation of the central nervous system. The skill level in the art is such low that the only treatments available to this day are drugs that are helpful in regulating Dopamine. Thus, a rejection under 35 U.S.C. 112, first paragraph is proper.

Stroke represents one of the most intractable medical challenges. Stroke is estimated to cause about 15% of deaths, behind only heart disease and cancer. Even those who survive normally suffer from persistent damage, including motor and speech disturbances and/or convulsions. Despite a tremendous effort to resolve these problems, cerebrovascular therapy as so far been limited to trying to prevent further damage in areas on the margins of the ischemic focus, thus trying to maintain adequate perfusion in remaining intact areas, and thereby limit progressive infarction. This is generally done surgically. Standard pharmaceutical treatment, such as antiarrhythmics

and antithrombotics don't get at the cause of the stroke or the damage caused, but are mostly done to insure adequate cardiac functioning.

Effective acute drug treatment of the stroke itself has so far proved to be beyond the reach of medical science. Major efforts have certainly been pressed in the area of neuroprotective therapeutics. Those studied have included use of Ca antagonists such as Levemopamil and flunarizine, to suppress neuronal calcium influx; NMDA antagonists (both competitive, such as APV and CPP, and non-competitive such as chlorpromazine, ifenprodil and Mg salts) as well as AMPA and kainate antagonists to block post-ischemic receptor-operated calcium channels; attempts to block arachidonic acid cascade or elimination of its metabolic products with agents such as lipogenase inhibitors and thromboxane; use of free oxygen radical scavengers such as superoxide dismutase, alpha-tocopherol, or allopurinol to inhibit the lipid peroxidation that damages cell membranes, which may indirectly help prevent intracellular calcium overload; anti-edema agents such as corticosteroids; use of 5-HT_{1A} receptor agonists to suppress 5-HT concentrations in the hippocampal extracellular space; use of CRF receptor antagonists to inhibit excitotoxic brain damage; use of serotonin 1A agonists such as ipsapirone, or adenosine modulators such as vinpocetine, to stimulate adenosine, which may act as a protective agent by hyperpolarizing the postsynaptic neuron; use of platelet aggregation inhibitors such as prostacycline and ticlopidine, and other approaches as well.

Despite this vast outpouring of research, the skill level in this art is sufficiently low relative to the difficulty of the task that obtaining a neuroprotective treatment of stroke

was, as of the filing date, not yet possible. Hence, accomplishing such a goal involves more than routine experimentation. As evidence for this, there is cited Chalmers (TiPS Vol 17, pages 166-172 April 1996), which states flatly on page 170 that, "At present, there are no effective neuroprotective agents that can clinically ameliorate the effects of stroke in humans." For example, Pentoxifylline has been one of the most intensely studied, with dozens of studies published on its properties. It appears to have a wide variety of effects on leucocytes, erythrocytes, neutrophils, plasma fibrinogen levels. These result in a wide-ranging ability to increase blood flow, resulting in effectiveness in some vascular disorders, especially intermittent claudication. Research with different administration methods, or different subcategories of stroke may well result in the discovery of how to get this drug to work, but the slowness and difficulty of this research shows clearly that this involves undue, not routine experimentation. Applicants' compounds have been subjected to far less study.

Cardiovascular disorders embrace a vast array of problems, many of which are contradictory to others. Thus, it covers hypertension and hypotension. It covers various types of arrhythmias; angina pectoris; the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias; ischaemic heart disease including congestive heart failure and myocardial infarction; stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCA); elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol; arteriosclerosis, peripheral vascular disease,

cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. No one compound --- let alone a genus of trillions of compounds, could possibly be effective against such disorders generally.

6. Claims 62-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In claims 62 and 65, it has been recited a method of treating memory impairment due to neurodegenerative disease or due to acute neurodegenerative disorder, but the specification is not enabled for such a scope.

There is no such an agent, which can treat neurodegenerative diseases (disorders) generally. That is because neurodegenerative diseases are extremely varied in origin and nature of effect. The origin and the nature of many neurodegenerative diseases such as Huntington's disease, Pick's disease, Frontotemporal dementia, Cerebro-Oculo-Facio-Skeletal (COFS) syndrome (cranofacial and skeletal abnormalities), Motor neuron disease (muscle weakness), Corticobasal ganglionic degeneration, Creutzfeldt-Jacob disease (fatal disease), Dementia with Lewy bodies, and Progressive supranuclear palsy Dementia are different one from the other. Many neurodegenerative disorders are untreatable to this day.

The symptoms and nature of these diseases are also different one from the other. It can be shown that many of these neurodegenerative disorders have different origin and nature of effect. Some neurodegenerative disorders are hereditary (Charcot-Marie-Tooth disease). Many neurodegenerative diseases vary in how they affect the body and its functions. Diseases such as Cerebral palsy, and Parkinson's disease affect the movement of the patient. Diseases such as Alzheimer's disease affect the memory of the patient.

7. Claims 68-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating allergic, does not reasonably provide enablement for inflammatory disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. In claim 68, it has been recited a method of treating inflammatory diseases in general, but the specification is not enabled for such a scope.

Enablement for the scope of "inflammatory disease" generally is not present. For a compound or genus to be effective against inflammation generally is contrary to medical science. Inflammation is a process which can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin,

C3a, C5a, histamine, assorted leukotrienes and cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

Inflammation is the reaction of vascularized tissue to local injury; it is the name given to the stereotyped ways tissues respond to noxious stimuli. These occur in two fundamentally different types. Acute inflammation is the response to recent or continuing injury. The principal features are dilatation and leaking of vessels, and recruitment of circulating neutrophils. Chronic inflammation or "late-phase inflammation" is a response to prolonged problems, orchestrated by T-helper lymphocytes. It may feature recruitment and activation of T- and B-lymphocytes, macrophages, eosinophils, and/or fibroblasts. The hallmark of chronic inflammation is infiltration of tissue with mononuclear inflammatory cells. Granulomas are seen in certain chronic inflammation situations. They are clusters of macrophages which have stuck tightly together, typically to wall something off. Granulomas can form with foreign bodies such as aspirated food, toxocara, silicone injections, and splinters.

Otitis media is an inflammation of the lining of the middle ear and is commonly caused by Streptococcus pneumoniae and Haemophilus influenzae. Cystitis is an inflammation of the bladder, usually caused by bacteria. Blepharitis is a chronic inflammation of the eyelids that is caused by a staphylococcus. Dacryocystitis is inflammation of the tear sac, and usually occurs after a long-term obstruction of the nasolacrimal duct and is caused by staphylococci or streptococci. Preseptal cellulitis is inflammation of the

tissues around the eye, and Orbital cellulitis is an inflammatory process involving the layer of tissue that separates the eye itself from the eyelid. These life-threatening infections usually arise from staphylococcus. Hence, these types of inflammations are treated with antibiotics.

Certain types of anti-inflammatory agents, such as non-steroidal anti-inflammatory medications (Ibuprofen and naproxen) along with muscle relaxants can be used in the non-bacterial cases. The above list is by no means complete, but demonstrates the extraordinary breadth of causes, mechanisms and treatment (or lack thereof) for inflammation. It establishes that it is not reasonable to any agent to be able to treat inflammation generally.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-33 and 37-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention:

a. Claim 1 and claims dependent thereon are rejected because in claim 1 or elsewhere in the claims the phrase "combinations thereof" is not clear. The substituents (halogen or hydroxy) are independent and can't be combined. One skilled in the art

would know that "alkyl" can be substituted by halogen, by hydroxy, or by both hydroxy and halogen. It is recommended that applicants delete "combinations thereof" from the claims.

b. In claim 1 (e.g. page 67, line 13) or elsewhere in the claims, the term C_{2-4} acyl" is not clear. Is the carbon atom from "acyl" included in the carbon count or not?

c. In claims 1, 33, 34, 37, 45, 54, 57, 62, 65, 68 and 71, the chemical structures are represented by two different notations. For example in claim 1, "Formula I " and "I", in claim 37 "formula I^c " and "I^c", but the notations are not consistent (one is roman number and the other one is in capital letter.

d. Claim 47 is rejected because it failed to narrow down the limitations of claim 46. Claim 46 that depends on claim 45 recites "patient is human" and claim 47 that depend on claim 46 recites "said patient is suffering from memory impairment." It is clear that the term "patient" in claim 46 refers to a person suffering from cognition impairment, thus claim 47 does not narrow down the limitations of claim 46.

e. Regarding claim 71, the phrase "particularly" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

f. Regarding claim 71, the term "e.g." renders the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Objection

9. Claims 35-36 and 74 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kahsay Habte, Ph. D. whose telephone number is (703) 308-4717. The examiner can normally be reached on M-F (9.00AM- 5:30PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 703-308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Kahsay Habte, Ph. D.
Examiner
Art Unit 1624

Mukund J. Shah
Supervisory Patent Examiner
Art Unit 1624

KH
June 12, 2003